May 13, 2021

Division of Dockets Management (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. FDA-2021-N-0270-0001
Endocrinologic and Metabolic Drugs Advisory Committee; Notice of Meeting; Establishment of a Public Docket; Request for Comments

JDRF is pleased to submit comments to the Food and Drug Administration ("FDA" or "Agency") regarding the Federal Register notice, "Endocrinologic and Metabolic Drugs Advisory Committee Notice of Meeting; Establishment of a Public Docket; Request for Comments" which appeared in the Federal Register on April 1, 2021.

ABOUT TYPE 1 DIABETES

Type 1 diabetes is an autoimmune disease that strikes children and adults suddenly and can be fatal. Until a cure is found and in order to stay alive, people with type 1 diabetes require lifelong and continuous insulin therapy coupled with continuous blood sugar monitoring. Too much insulin can result in seizures, coma, or death from hypoglycemia and too little insulin over time leads to devastating kidney, heart, nerve, and eye damage from hyperglycemia.

Despite advances in insulin and technologies to continuously deliver insulin and monitor blood glucose levels, recent data from the T1D Exchange Clinic Network show that the majority of people in the US are not achieving ADA recommended Hemoglobin A1c (HbA1c) targets with particularly high levels in adolescents and young adults.[1] The average patient spends 7 hours a day hyperglycemic and over 90 minutes hypoglycemic.[2]

People with diabetes desperately need continued access to improved therapies designed to prevent, cure, and assist in the management of this difficult disease and prevent its life-threatening short and long-term complications.

ABOUT JDRF

JDRF is the leading global organization funding type 1 diabetes research. Our mission is to accelerate life-changing breakthroughs to cure, prevent and treat type 1 diabetes and its complications and we collaborate with a wide spectrum of partners in the community to achieve this mission. Founded in 1970 by parents of children with type 1 diabetes, JDRF has invested over $2 billion in research since its inception.

The JDRF T1D Fund is a venture philanthropy fund launched in 2016 to activate a robust life sciences investment market aimed at delivering solutions to people living with or at risk of

[1] Foster, et al. State of Type 1 Diabetes Management and Outcomes from the T1D Exchange in 2016-2018. Diabetes Technol Ther 2019;21(2):66-72. *Diabetes Technol Ther*. 2019;21(4):230. doi:10.1089/dia.2018.0384.correx

[2] Tamborlane WV, et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med. 2008 Oct 2;359(14):1464-76. doi: 10.1056/NEJMoa0805017. Epub 2008 Sep 8. PMID: 18779236.
Bode, et al. Glycemic characteristics in continuously monitored patients with type 1 and type 2 diabetes: normative values. Diabetes Care. 2005. 28:2361-6.

developing T1D. The T1D Fund previously invested in Provention Bio to facilitate the acquisition and clinical development of T1D relevant assets, but no longer has any financial interest in the company. JDRF is the parent organization of the T1D Fund; however, the T1D Fund is separately governed and independently managed.

JDRF'S COMMENTS

Type 1 diabetes (T1D) is a chronic autoimmune disease with significant morbidity and mortality and burden to patients and their caregivers. There is an urgent need for safe and effective therapies for people at high risk for T1D that can modify the disease course and delay the onset to reduce the high burden of living with T1D and the devastating short- and long-term complications of the disease. The delay in onset of T1D of two years demonstrated by teplizumab, the product being considered by the Advisory Committee on May 27, 2021, is clinically meaningful.

Unmet Needs and Disease Burden are Significant for People with T1D

The mainstay of T1D disease management, insulin therapy, has been around for almost a hundred years and, while life-sustaining, it has significant medical risks, poor clinical outcomes, and high patient burdens. There are no available disease modifying therapies for T1D that impact the fundamental autoimmune defects which damage the beta cells in the pancreas and the body's ability to produce insulin.

In someone without T1D, through complex mechanisms and signaling with other cells, the beta cells automatically maintain normal glucose levels by secreting the right amount of insulin at the right time where it's needed in the body. To stay alive, people with T1D must inject or infuse insulin exogenously. This non-physiologic method of insulin replacement is far inferior. Even with the best tools, insulin delivered exogenously has significant delays in action and it's dosing is far less precise than insulin secreted from the beta cells. As a result, exogenous insulin replacement therapy delivers both too much and too little insulin on a daily basis.

Too much insulin and a person experiences the immediate and dangerous consequences of low blood sugar, or hypoglycemia, such as inability to concentrate, loss of consciousness, seizures, and death. Too little insulin over time leads to long-term complications such as kidney failure, heart attacks, vision loss, and nerve damage from high blood sugar, or hyperglycemia. The burden of T1D management falls almost entirely on people with T1D and their families. Insulin's very narrow therapeutic window is impacted by many factors such as diet, activity level, stress, and illness. It also can behave differently each day and requires 24 hours a day vigilance. Moreover, with the relatively younger age of onset and life-long need for insulin, the potential for complications at an earlier age is precedented and the high burden of T1D is long-lasting.

Overall outcomes for the population of people with T1D are alarming. People with T1D have a decreased life expectancy impacted by both duration of disease and HbA1c levels.[3,4] Even with diligent monitoring, the majority of people with T1D in the United States do not achieve American Diabetes Association (ADA) recommended HbA1c targets. The T1D Exchange Registry shows us that within specialty diabetes clinics in the U.S. that are a part of the Registry, approximately four in five children and two in three adults do not meet HbA1c targets.[5] This same worrisome trend was seen in a large retrospective analysis of an electronic health record (EHR) database from

[3] Rawshani, et al. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. Lancet, 2018

[4] Lind M, et al. Glycemic control and excess mortality in type 1 diabetes. N Engl J Med. 2015 Feb 26;372(9):880-1. doi: 10.1056/NEJMc1415677. PMID: 25714168.

[5] Miller KM, et al.; T1D Exchange Clinic Network. Current state of type 1 diabetes treatment in the U.S.: updated data from the T1D Exchange clinic registry. Diabetes Care 2015;38:971–978 pmid:25998289

real world clinical practice.[6] What is even more concerning is that HbA1c levels steadily increase, or worsen, among individuals with T1D aged 7-19 before a gradual decline, or improvement, until around age 30. On average, glucose control is significantly worse among teenagers and young adults.[7] An important aspect to highlight is that the average person with T1D spends 7 hours a day hyperglycemic and over 90 minutes per day hypoglycemic.[5] Rates of severe hypoglycemia, those cases where the person with T1D needs the assistance of another person, are much too high with recent reports of the prevalence as high as 35% in people with type 1 diabetes.[8,9]

Rates of diabetic ketoacidosis, a serious and life-threatening condition caused by insulin insufficiency that often requires hospitalization, are very high at T1D clinical diagnosis. In children diagnosed with T1D from 2010-2017 in Colorado, 58% had DKA at diagnosis[10] and this is associated with worsening glycemic control over time, independent of demographic, socioeconomic, treatment-related factors and baseline fasting C-peptide levels.[11,12]

Data from National Institute of Health's DCCT (Diabetes Control and Complications Trial) and EDIC (Epidemiology of Diabetes Interventions and Complications) randomized, longitudinal studies have shown that intensive blood glucose control decreases the development of diabetes-related complications such as heart, eye, kidney, and nerve disease and also lengthens life.[13,14] With the state of diabetes care reviewed above, people with T1D are at high risk of complications. About a quarter of people with T1D will progress to end-stage renal disease (ESRD)[15] requiring dialysis or kidney transplant. More than half of people with T1D show signs of diabetic retinopathy after 20 years with T1D.[16] Cardiovascular disease (CVD) events are more common and occur earlier in patients with T1D than those without diabetes and it has been reported that the age adjusted relative risk for CVD in T1D is about 10 times that of the general population.[17] Severe hypoglycemia has also been linked to extreme cases of arrythmia and autonomic failure causing

[6] Pettus, et al., Incidences of Severe Hypoglycemia and Diabetic Ketoacidosis and Prevalence of Microvascular Complications Stratified by Age and Glycemic Control in U.S. Adult Patients With Type 1 Diabetes: A Real-World Study. Diabetes Care 2019 42: 2220-2227.

[7] Laffel LM, et al. Effect of Continuous Glucose Monitoring on Glycemic Control in Adolescents and Young Adults With Type 1 Diabetes: A Randomized Clinical Trial. JAMA. 2020 Jun 16;323(23):2388-2396. doi: 10.1001/jama.2020.6940. PMID: 32543683; PMCID: PMC7298603.

[8] Pinés Corrales PJ, et al. Prevalence of severe hypoglycemia in a cohort of patients with type 1 diabetes. Endocrinol Diabetes Nutr. 2021 Jan;68(1):47-52. English, Spanish. doi: 10.1016/j.endinu.2020.01.002. Epub 2020 Apr 26. PMID: 32349942.

[9] Gubitosi-Klug RA, Braffett BH, et al. Erratum. Risk of Severe Hypoglycemia in Type 1 Diabetes Over 30 Years of Follow-up in the DCCT/EDIC Study. Diabetes Care 2017;40:1010–1016 - January 01, 2021

[10] Alonso GT, et al. Diabetic Ketoacidosis at Diagnosis of Type 1 Diabetes in Colorado Children, 2010-2017. Diabetes Care. 2020 Jan;43(1):117-121. doi: 10.2337/dc19-0428. Epub 2019 Oct 10. PMID: 31601639; PMCID: PMC6925579.

[11] Duca LM, et al. Diabetic ketoacidosis at diagnosis of type 1 diabetes and glycemic control over time: The SEARCH for diabetes in youth study. *Pediatr Diabetes*. 2019;20(2):172–179. doi:10.1111/pedi.12809

[12] Shalitin S, et al. Ketoacidosis at onset of type 1 diabetes is a predictor of long-term glycemic control. Pediatr Diabetes. 2018 Mar;19(2):320-328. doi: 10.1111/pedi.12546. Epub 2017 Jun 1. PMID: 28568379.

[13] Diabetes Control and Complications Trial Research Group, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993 Sep 30;329(14):977-86. doi: 10.1056/NEJM199309303291401. PMID: 8366922.

[14] Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. "Epidemiology of Diabetes Interventions and Complications (EDIC). Design, implementation, and preliminary results of a long-term follow-up of the Diabetes Control and Complications Trial cohort." *Diabetes care* vol. 22,1 (1999): 99-111. doi:10.2337/diacare.22.1.99

[15] Bakris GL, Molitch M. Are All Patients With Type 1 Diabetes Destined for Dialysis if They Live Long Enough? Probably Not. Diabetes Care. 2018 Mar;41(3):389-390. doi: 10.2337/dci17-0047. PMID: 29463664.

[16] Kytö JP, et al. Decline in the cumulative incidence of severe diabetic retinopathy in patients with type 1 diabetes. Diabetes Care. 2011 Sep;34(9):2005-7. doi: 10.2337/dc10-2391. PMID: 21868777; PMCID: PMC3161282.

[17] de Ferranti SD, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. Circulation. 2014 Sep 23;130(13):1110-30. doi: 10.1161/CIR.0000000000000034. Epub 2014 Aug 11. PMID: 25114208.

cardiac arrest.[18] In addition, the risk of microvascular and macrovascular complications increases with longer duration of disease.[19]

The high and constant burden of living with T1D coupled with the poor outcomes and high rates of complications underscore the critical need for therapies that change the course of the disease, including delaying progression.

Delaying Onset of Clinical T1D by Two Years is Clinically Meaningful

A delay in onset in T1D of at least two years will likely have long-term benefits for glycemic control, and the reduction in acute and long-term complications would have a tremendous impact on the daily lives of people with T1D, their families and our overall health system. Simply put, a two-year delay in T1D onset is clinically meaningful.

An intervention that delays clinical onset in those at high risk for developing T1D means delaying dependence on exogenous insulin therapy which, as detailed above, carries significant risks. The risk of hypoglycemia – which includes inability to concentrate, loss of consciousness, seizures, and death – would be completely eliminated during that time period.

Moreover, a delay in T1D onset would reduce two major risk factors for longer-term complications, duration of T1D and higher HbA1c levels.

- A two-year delay in T1D onset would reduce the overall duration of the disease, reducing the duration of exposure to hyperglycemia in this life-long disease.

- Extensive evidence shows that children who are known to be at high risk for T1D and are being monitored for clinical onset have a less severe clinical disease course, including a lower incidence of DKA and hospitalization at diagnosis.[20]

- Delaying T1D clinical onset from its current peak incidence range of adolescence to early adulthood or later could have profound long-term benefits of improved outcomes with respect to complications, quality of life and life expectancy. Outcomes in young people with T1D are particularly poor, as discussed above, so any delay beyond that life stage will be especially impactful.[21]

Beyond the important and significant clinical benefits, any person with T1D and their family can convey the profoundly positive impact a delay in onset would have on their daily lives, and how they feel, function, and survive. It would free them from the constant burden and stress of glucose monitoring and insulin administration. It would free them from the worry and fear of short- and long-term complications while giving them the opportunity to learn more about disease management. And it would allow them to live life like those of us without T1D are able to do. That is clinically meaningful.

JDRF is pleased that teplizumab received Breakthrough Therapy designation from the Agency, which is a recognition of the data presented and the unmet need. If determined by FDA to be safe and effective, teplizumab can aid in addressing the stark unmet need for disease modifying

[18] Snell-Bergeon, et al. Hypoglycemia, diabetes, and cardiovascular disease. *Diabetes technology & therapeutics* vol. 14 Suppl 1,Suppl 1 (2012): S51-8. doi:10.1089/dia.2012.0031

[19] Thaddäus, et al. Risk of Microvascular Complications and Macrovascular Risk Factors in Early-Onset Type 1 Diabetes after at Least 10 Years Duration: An Analysis of Three Population-Based Cross-Sectional Surveys in Germany between 2009 and 2016, *International Journal of Endocrinology*, vol. 2018. Article ID 7806980, 11 pages, 2018.

[20] Elding Larsson H, et al; TEDDY Study Group. Children followed in the TEDDY study are diagnosed with type 1 diabetes at an early stage of disease. *Pediatr Diabetes*. 2014;15(2):118-126.

[21] Davis AK, et al; T1D Exchange Clinic Network. Prevalence of detectable C-Peptide according to age at diagnosis and duration of type 1 diabetes. Diabetes Care. 2015 Mar;38(3):476-81. doi: 10.2337/dc14-1952. Epub 2014 Dec 17. PMID: 25519448.

therapies and provide people at high risk for T1D and their families at least two more years without the burden and complications this disease brings. Therapies like these put us on the critical pathway to finding cures and, one day, preventing T1D entirely.

Thank you very much for your consideration of these comments. If you have questions, please contact Marjana Marinac, Senior Director of Regulatory Affairs for JDRF at mmarinac@jdrf.org or 202-465-4126.